

19. (reiterated) The method of Claim 18, wherein said RNA comprises 2-amino pyrimidine nucleotides.

B5 21. (amended) The method of Claim 15, wherein said polynucleotide comprises the sequence set forth in any of SEQ ID NO: 12 to SEQ ID NO:16.

23. (reiterated) The method of Claim 20, wherein said ligand comprises the sequence set forth in SEQ ID NO:12.

25. (amended) The method of Claim 15, wherein said polynucleotide ligand composition comprises two or more distinct sequences.

Ble 26. (amended) The method of Claim 23, wherein said polynucleotide ligand composition comprising distinct sequences bind to different epitopes of the virus.

#### REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1, 6, 8, 10, 12-16, 19, 21, 23, 25-26, the currently pending claims. Claims 2-5, 7, 9, 11, 17-18, 20, 22, and 24 have been canceled, without prejudice to refiling. Claims 1, 6, 8, 13-15, 21, 23 and 24 have been amended. No new matter is added.

The Office Action states that the distinct anti-viral sequences lack unity of invention because the sequences do not share a substantial structural feature disclosed as being essential to that utility. Applicants respectfully submit that the polynucleotides do share a common structural feature disclosed as essential to utility. As provided in the specification (page 6, line 20), the anti-viral polynucleotides were selected on the basis of specific binding to human cytomegalovirus, providing for a common structure. The fact that a virus may comprise multiple epitopes and proteins does not mean a lack of unity; it is well known in the art that virtually any complex biomolecule will comprise a plurality of sites for binding.

The polynucleotide ligands as presently claimed specifically recite an RNase resistant RNA ligand, lacking complementarity to the viral genome (see specification, page 7, lines 6-10). The ligands are not active on the basis of the sequence specificity, but rather on the three-dimensional

structure formed by the folding of the molecule, and the way that any chemical compound will form a tertiary structure having certain binding capabilities. The scope of the claims should be commensurate with standard chemical practice, and does not relate to the practice relating to polynucleotide sequences whose use resides in the sequences encoded by the polynucleotide.

Claim 15 and dependent claims thereon relates to a method of treating human cytomegalovirus infection, which method is searchable on the basis of the treatment method, and does not rely on the specific sequence of the polynucleotide ligand.

The Brief Description of the Drawings has been amended to recite the Figures as requested by the Examiner.

Claims 1-8, 12-21 and 25-26 have been rejected under 35 U.S.C. 112, first paragraph. Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112.

The claims have been amended to recite specifically an anti-human cytomegalovirus that lacks complementarity to a human cytomegalovirus genetic sequence. Applicants respectfully submit that a representative number of species has been provided. Regardless of current restriction practice, one cannot properly ignore data provided in the specification that is relevant to the claimed invention.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."<sup>1</sup>

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.<sup>2</sup>

The instant specification teaches how to select for polynucleotides having specific binding to human cytomegalovirus, and how to determine whether such polynucleotides suppress the virus

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<sup>1</sup> *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

<sup>2</sup> *Ex Parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Interf. 1986); and, *In re Wands*, 8

infection. Polynucleotides as claimed have the ability to suppress virus infection. To fall within the scope of the instant claims, the ligands must be able to suppress hCMV infection, bind to hCMV, lack complementarity to the hCMV genome.

The specification on page 10, line 13 discloses guidance for selecting polynucleotides through rounds of exponential enrichment. The specification gives guidance on how to determine whether a polynucleotide inhibits hCMV infection as set forth in the Examples, and in the specification, page 15, lines 12-24.

Specific examples of polynucleotide ligands meeting the requirements of the claims are provided, for example, in Tables 1 and 2, including L13, L19 and L66.

The Office Action states that there is no correlation between hCMV binding and antiviral activity. Applicants respectfully submit that in all cases, high specificity binding is a pre-requisite for consideration, due to the method of selection by viral SELEX. Naturally, not all ligands will bind to the same "epitope" of the virus, as one would not expect a population of antibodies raised to a virus to bind to the same epitope. The specificity of the polynucleotide ligands for hCMV, *i.e.* they do not bind to mouse CMV or HSV-1; is a benefit of the invention, and a desirable feature.

Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.3

As the court explained<sup>4</sup>:

"[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology

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USPQ2d 1400, 1404 (Fed. Cir. 1988).

<sup>3</sup> See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

<sup>4</sup> *In re Wands* 8 USPQ 2d at 1404

arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art, which routinely performs such long experiments.<sup>5</sup>

The claimed compositions relate to polynucleotide ligands that lack complementarity to human cytomegalovirus genetic sequence; bind to human cytomegalovirus; and inhibit human cytomegalovirus infection. The procedure for viral SELEX is laid out in detail, and screening for inhibition of viral infection is routine. The sequence of polynucleotides retaining biological activity is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay to determine the active variants, no undue experimentation is necessary.

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled

in the art would be able to practice the invention without undue experimentation.<sup>6</sup> Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."<sup>7</sup> As discussed above, numerous working examples have been provided.

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such technicians are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

There may be some non-functional variants within the genus defined by the claims. However, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained<sup>8</sup>:

"To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts.... More importantly, such a requirement would force

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<sup>5</sup> *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

<sup>6</sup> *In re Borkowski*, 164 USPQ at 645.

<sup>7</sup> *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

<sup>8</sup> *In re Angstadt*, 190 USPQ at 218.

an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

The claims of the instant application encompass sequences that have the ability to effectively suppress hCMV infection. In other words, in order to fall within a claim, a sequence must be able to suppress infection. *Thus, the claim language excludes ligands that do not exhibit this activity.*

In sum, the amount of experimentation required to identify polynucleotide ligands that lack complementarity to human cytomegalovirus genetic sequence; bind to human cytomegalovirus; and inhibit human cytomegalovirus infection would not be undue because a) a working example has been provided, b) guidance is given on how to test the sequences has been provided, and c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the active sequences.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1-2 and 4-5 have been rejected under 35 U.S.C. 102(b) as anticipated by Pan *et al.* Pan *et al.* discloses pools of RNA and RNA analogs having RSV neutralizing activity. The pending claims have been amended to recite a composition having anti-hCMV activity, which activity is not taught or suggested by Pan *et al.*

Claims 1-2 and 12 have been rejected under 35 U.S.C. 102(b) as being anticipated by Ecker *et al.* Ecker *et al.* teaches compounds inhibiting HIV infection. The pending claims have been amended to recite a composition having anti-hCMV activity, which activity is not taught or suggested by Ecker *et al.*

Claims 1-2, 4-6, 12-13, 15-19 and 25 have been rejected under 35 U.S.C. 102(b) as anticipated by Wang *et al.* Wang *et al.* teaches RNA sequences that have RSV neutralizing activity. The pending claims have been amended to recite a composition having anti-hCMV activity, which activity is not taught or suggested by Wang *et al.*

In view of the above amendments and remarks, withdrawal of the rejections is requested.

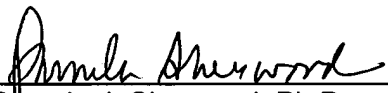
#### CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number BERK-005.

Respectfully submitted,

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## APPENDIX

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 3, line 17 to page 4, line 12, replace with the following rewritten paragraphs:

--[Figure 1. (A)] Figures 1A-1B. Figure 1B. Schematic representation of the evolution *in vitro* procedures to select RNA analogs that bind to HCMV particles. The pool of DNA molecules contained a randomized sequence of 40 nucleotides indicated as N. (Figure 1B) Increased binding affinity of the populations of RNA analogs during selection from cycle 0 to cycle 16. Binding assays were carried out with different concentrations of virus and a trace amount (<100 fmol) of ligands. The values of binding affinity were calculated by dividing the percentage of bound ligands with the concentration of HCMV used ( $\mu\text{g}$  protein /ml). Each point represents the mean of duplicate measurements.

[Figure 2.] Figures 2A-2B Binding affinity of the selected ligands to HCMV. (Figure 2A). 1 nM of different selected ligands were allowed to bind to different concentrations of HCMV particles. The values for the percentage of binding represent the mean of triplicate experiments and are not significantly different when 0.1 nM-5nM of ligands were used in the binding assays. (Figure 2B). 1 nM of radiolabeled L13 was allowed to bind to  $1 \times 10^5$  pfu/ml (about 30  $\mu\text{g}$  viral protein/ml) HCMV in the presence of different concentrations of unlabeled L13, L19, G<sub>0</sub>, and tRNA<sup>ser</sup>. The level of binding of L13 was calculated as the ratio of the percentage of bound radiolabeled L13 in the presence of other ligands over that obtained in the absence of these ligands. The values are the means of triplicate experiments. A value of 100% indicated that there was no competition between the binding of L13 and the other ligand molecules to HCMV.

[Figure 3.] Figures 3A-3D. Effect of the ligands on plaque formation (Figure 3A and Figure 3C) and particle production (Figure 3B and Figure 3D).  $1 \times 10^5$  pfu/ml HCMV (AD169) or HSV-1 (F) was incubated in DMEM media alone or in the presence of different concentrations of G<sub>0</sub>, L13, L19 at 37°C for 15 mins before used to infect HFFs at MOI of 0.005 (for plaque assay) or 0.3 (for titer assay). The levels of viral titer and plaque formation were calculated as the ratio of the titers and plaque numbers assayed from experiments with HCMV incubated in the presence of the ligands over those from experiments with HCMV incubated in DMEM alone, respectively. The values are the means of triplicate experiments.--

Page 4, line 29, to page 5, line 6, replace with the following rewritten paragraph:

--[Figure 9] Figures 9A-9D. Effect of the ligands on plaque formation (A and C) and particle production (B and D) of HCMV (AD169) (A and B) and herpes simplex virus 1 (F) (C and D) in

human foreskin fibroblasts (HFFs).  $1 \times 10^5$  PFU/ml HCMV (AD169) or HSV-1 (F) was incubated in DMEM media alone or in the presence of different concentrations of G<sub>0</sub>, L31, L66 at 37°C for 15 mins before being used to infect HFFs at MOI of 0.02 (for plaque assay) or 0.5 (for titer assay). The levels of viral titer and plaque formation were calculated as the ratio of the titers and plaque numbers assayed from experiments with HCMV incubated in the presence of the ligands over those from experiments with HCMV incubated in DMEM alone, respectively. The values are the means from triplicate experiments.--

#### IN THE CLAIMS

1. (amended) An [antiviral] anti-human cytomegalovirus RNAse resistant RNA polynucleotide ligand composition of from 15 to 100 nucleotides in length, and which lacks complementarity to said human cytomegalovirus genetic sequence; binds to said human cytomegalovirus; and inhibits said human cytomegalovirus infection.

6. (amended) The polynucleotide ligand of Claim 5, wherein said RNA comprises 2-amino pyrimidine[s] nucleotides.

8. (amended) [The polynucleotide ligand of Claim 7] An anti-human cytomegalovirus polynucleotide ligand, wherein said polynucleotide comprises the sequence set forth in any of SEQ ID NO:1 to SEQ ID NO:28, or SEQ ID NO:36 to SEQ ID NO:41] 12 to SEQ ID NO:16

13. (amended) The polynucleotide ligand composition of Claim 12, wherein said polynucleotide ligand[s] composition comprises two or more distinct sequences.

14. (amended) The polynucleotide ligand composition of Claim 13, wherein said [ligands] polynucleotide ligand composition comprising distinct sequences bind to different epitopes of the virus.

15. (amended) A method of treating [viral] human cytomegalovirus infection, the method comprising:

administering a dose of an [antiviral] anti-human cytomegalovirus RNAse resistant RNA polynucleotide ligand composition at a dose sufficient to decrease said [viral] cytomegalovirus infection, wherein said polynucleotide ligand is from 15 to 100 nucleotides in length, and which lacks

complementarity to said human cytomegalovirus genetic sequence; binds to said human cytomegalovirus; and inhibits said human cytomegalovirus infection.

21. (amended) The method of Claim 15, wherein said polynucleotide comprises the sequence set forth in any of SEQ ID NO:[1 to SEQ ID NO:28, or SEQ ID NO:36 to SEQ ID NO:41] 12 to SEQ ID NO:16.

25. (amended) The method of Claim 15, wherein said polynucleotide ligand[s] composition comprises two or more distinct sequences.

26. (amended) The method of Claim 23, wherein said [ligands] polynucleotide ligand composition comprising distinct sequences bind to different epitopes of the virus.